(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 December 2002 (27.12.2002)

PCT

(10) International Publication Number
WO 02/102129 A2

(51) International Patent Classification: Not classified

(21) International Application Number: PCT/BR02/00001

(22) International Filing Date: 3 January 2002 (03.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PI 0100334-8 17 June 2001 (17.06.2001) BR

(71) Applicant *(for all designated States except US)*: **DIFFUCAP CHEMOBRAS QUIMICA E FARMACEUTICA LTDA.** [AR/BR]; Rua Goiás, 1232, Quintino Bocaiuva, CEP-021380-010, RJ (BR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **MOLENDA FERREIRA AMADO, Elizabeth** [AR/AR]; Chacabuco, 96, 2° Piso, AR-1069 Buenos Aires (AR). **RAFAEL DE SOUZA, Fernando** [AR/AR]; Chacabuco 96° Piso, AR-1069 Buenos Aires (AR).

(74) Agent: **OCTÁVIO & PEROCCO S/C LTDA.**; Av. Indianópolis, 1811, Planalto Paulista, CEP-04063-003 São Paulo, SP (BR).

(81) Designated States *(national)*: AU, CA, CN, CZ, HR, HU, JP, KP, KR, LU, MX, NO, NZ, PL, RO, SG, US, ZA.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

**Published:**
— *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 02/102129 A2

(54) Title: PROCESS FOR PREPARATION OF PROGRAMMED LIBERATION COMPOSITION WITH VENLAFAXINE AND THE RESULTING PRODUCT

(57) Abstract: Process for the preparation of programmed liberation compositions with venlafaxinee and the resulting product, from which the resulting product allows a better absorption of the active principle and a drastic decrease of the adverse effects, due to the preparation methodology. The formulation comprises a first phase, in which the non-active cores are elaborated as spherical micro granules, from sugar and starch. In the second phase, it is added to them the active drug, as impalpable powder, utilizing as binding, a povidone alcoholic solution. In the third phase, it is applied the coating on the micro granules that contain the active drug. At last, in the fourth phase, it is made the encapsulation of the recoated micro granule.

"PROCESS FOR PREPARATION OF PROGRAMMED LIBERATION COMPOSITION WITH VENLAFAXINE AND THE RESULTING PRODUCT"
Descriptive Report

The present invention relates to a new formulation of programmed liberation capsules with Venlafaxine (*) HC1 active principle, as well as the resulting product, which presents a larger absorption of active principle and a drastic reduction of the adverse effects.

(*) 1 – [2-(Dimethylamine) –(4 –methoxyphenyl) ethyl]ciclohexanol

Various procedures are utilized for the preparation of programmed liberation pharmaceutical products. Among these, the slowly soluble matrix tablets may present the disadvantage of suffering pyloric retention, what prevents foreseeing, in a determined moment, the place in the digestive segment in which they are, thus causing the indetermination of the dissolution profile.

The process of the present invention includes the elaboration of prolonged action micro granules (PAM) that contains the active principle. These granules are placed, in large amount, within capsules that, upon separating in the gastric lumen, allow the dispersion of the micro granules by all the available volume, liberating the active principle in an independent form one of the other, acquiring the maintenance of a defined dissolution profile.

The elaboration process allows, further avoiding an additional difficulty that presents the Venlafaxine in programmed liberation preparations, such as its high solubility. Once the programmed dissolution is obtained by means of the deposit of a tissue around the micro granules, this must have a sufficient thickness to regulate in a proper form its dissolution speed.

The objective of the present invention is developing an elaboration methodology that includes prolonged action micro granules containing Venlafixine, and in such a way that allows regulating the thickness of the involving tissue, for getting the adequate dissolution profile of the active principle and, consequently, a better absorption of the active principle and decrease of its adverse effects.

Regarding the antecedents of the present invention, some previous patents are know, in which were developed methods of MAP elaboration containing Venlafaxine HC1:

In these patents, the cores are elaborated from the mixture of the active drug with microcrystalline cellulose, which is crushed and granulated utilizing hydroxypropilmetylcellulose dispersed in water as binding, such a dispersion may b e prepared in-site of previous form This wet mass is extruded, shaped into spheres, dried and purified (to select granulometries), the micro granules being obtained with incorporated and without coating active drug, with the property of " immediate liberation".

In these same patents, it is also claimed the elaboration of cores without the presence of hydroxipropilmethylcellulose, although this is utilized soon after, duly mixed with ethyl cellulose, in the after phase of coating application.

To get the "programmed liberation" properties, the micro granules are covered with a tissue, by the deposition of a mixture of ethyl cellulose and hydroxypropilmethylcellulose. This process is realized in a liquefied bed by aspersion of an ethyl cellulose solution and hydroxypropilmetylcellulose in a solvent constituted of a mixture of methylene chloride and methanol.

The main object of the present invention is a new formulation of prolonged liberation capsules containing the Venlafaxine HC1 active principle, characterized by presenting a Bioavailability in humans of 2,279 mg.h/mo, and by comprising the following elaboration procedure:

I – Elaboration of the non-active core. These cores are elaborating by wetting sugar crystals in a coating boiler with a diluted solution of sugar in water. These wet crystals are powdered with cornstarch, to favor the formation of spheres by the turbulent motion of the crystals within the boiler, and to eliminate the wet excess. These spherical wet cores are dried in a drying stove with forced hot air circulation and after that purified to be classified by their granulometry.

II – Elaboration of the active core. The inert cores elaborates in the previous phase, dried, purified and with adequate granulometry, are placed in a coating boiler of adequate capacity, where they are wetted with a Povidon alcoholic solution (generally an isopropyl alcohol). When the desired stage of humidity is attained, we begin the powdering of the product within the boiler with Venlafaxine HC1 previously grinded until impalpable powder. When the incorporation of the active principle is finished, the micro granules are passed by stainless steel sieve with appropriated mesh and after that they are dried in the same moving boiler , with hot air blast, or in forced hot air drying stove.

III – Application of the coating. In the present invention acetone solutions or Ethyl cellulose acetone-alcoholic, to which was aggregated an adequate plasticizer to low the vitreous transition temperature, avoiding thus the formation of breakable membranes.

Next are presented two technological possibilities for the obtainment of the membrane that covers the micro granules of quality and thickness enough to attain the desired programmed dissolution profile.

- With coating boiler. In the same boiler in which are elaborated the active micro granules, the same are powdered with the same Ethyl cellulose solution. The evaporation of the solvent leaves the micro granule coated with a fine coat of plasticized ethyl cellulose. The thickness of the coat is regulated through the quantity of applied solution. Is product is left to dry by rotation in a boiler with hot air blast, or then in stove with forced hot air. It is realized the deposition of crescent quantities of the coating tissue, until it is obtained the desired in vitro dissolution.
- Liquefied bed with Wurster. In this case, it is required a previous preparation of "naked" micro granules, with those obtained in the first phase. Due to the energetic motion within the Wurster, the micro granules are hardened applying to them, in the coating boiler, first a PVP pre-coat, and then ethyl cellulose. At least, it is ended the powdered coating, on the micro granules placed in the liquefied bed, the same solution that is applied in the coating boiler.

The differences between both steps are the following:

a) In the Wurster, the application of the coating is more effective, obtaining equal tissue thickness , with less quantities of applied solution.
b) The processes are more reproductive in the Wurster than in traditional coating boilers. Nevertheless, in these last, the product is more accessible, because an eventual difficulty in the process may be detected and corrected faster.
c) In the conventional coating boilers, the product is not submitted to mechanical stress that the liquefied bed suffers, obtaining a smaller production of powder, not desired.

Comparing the current method with the previous ones, we describe below the components of the different procedures:

| Previous | Current |
|---|---|
| Venlafaxine HC1 | Venlafaxine HC1 |
| Microcrystalline Cellulose | Non active cores (sugar, starch) |
| Hydroxypropyltmethylcellulose | PVP |
| | Talk |
| Ethyl cellulose | Ethyl cellulose |
| | Plastcizer |

As to the difference of the elaboration method:

| Previous | Current |
|---|---|
| Elaboration of the (active) core<br>Mixture of: drug + microcrystalline cellulose + hydroxypropylmethylcellulose/wetting/kneaded/ extrusion/shaping into sphere | Elaboration of the (non active) core:<br>Application of starch on sugar crystals, using sugar in water solution as binder |
| | Elaboration of the (active) core:<br>Application of grinded drug on non-active cores, using PVP alcoholic solution as binder. |
| Coating:<br>Ethyl cellulose + hydroxypropylmethylcellulose / Deposited from a solvent constituted by methanol-methylene chloride. | Coating:<br>Ethyl cellulose + Plasticizer / Deposited from a solvent constituted by acetone or acetone + isopropyl alcohol. |
| Employed machine in coating: Only liquefied bed | Employed machine in coating: liquefied bed or coating boiler. |

As it regards an extremely soluble drug, the dissolution profile of the same is exclusively regulated by the quality and thickness of the coating tissue. Thus, both technologies, the previous and the current one, may led to similar products from the point of view of its bioavailability. However, it was possible demonstrating, in a comparative study made in humans, that the process of the present invention leads to the obtainment of a superior product, because of its better absorption, than that obtained by previous methods.

As referred early, the process of the present invention is more versatile, due to the fact that not every active principle may be elaborated by kneading, extrusion and shaping it into sphere method. Particularly, if the required concentration is so high that it presents a very narrow margin for the aggregate of excipients, the kneading, extrusion and shaping it into sphere could not be possible.

Going now to a more detailed description of the present invention, it is made through the following examples that show how it can be put to practice:

1.- Batch: PE 9942 – First phase

400 grams of active drug were kneaded and applied, in a coating boiler, on 200 grams of sugar and starch cores. As binder, it was utilized PVP solution at 5% in

isopropyl alcohol. During the process, it was kept constant the granulometry of the product, by the depuration and classification by sizes, periodically made. Once the entire active drug was applied, it was made the coating of the product with 100 grams talk, using additional PVP solution. The total PVP solution utilized was 800 ml. The product was dried overnight at 45C, and made the corresponding controls, that included:

Weight: 480 grams

Title: 450.7 mg/g

Dissolution: 103%

Capability of capsule: N° 0 = 461.6 mg/capsule

N° 1 = 333.2 mg/capsule

2.- Batch: PE 9942 – Second phase

From the batch obtained in example 1, 300 grams of micro granules were separated and placed in an experimental equipment of liquefied bed. In this equipment, were applied crescent quantities of plasticized ethylcellulose with 10%, calculated on Mygliol contained solids. The ethyl cellulose was at 3% in acetone and the operative conditions of the equipment were those traditional for this type of coating. During the process of coating, it was noted that it was necessary periodically powdering the product with talk, to diminish the static load, and the mechanical conditions occasioned the rupture of some of the micro granules. With a total applied volume of about 2.920 liters/kg of micro granules, the value and the dissolution profile were the following:

Value: 409.54 mg/g

Dissolution:

After 1 hour : 20.0%

After 4 hours : 58.0%

After 8 hours : 75.7%

After 24 hours : 96.7%

3.- Batch: PE 10326 – First phase

29.500 kg of active drug were kneaded and incorporated, in a coating boiler of adequate size, on 14.750 kg of sugar and starch cores. With binding solution, were used approximately 30 liters of PVP solution at 5% in isopropyl alcohol. The sizes were equalized, as possible, and the obtained product was coated with 8.850 kg of talk, utilizing 5 additional liters of PVP solution. The product was dried in stove at

45°C and, once analyzed the balance (yield) of drug, it was applied a pre cover of coating in the same boiler: 4 liters of PVP at 10% in isopropyl alcohol were incorporated and, after this, 24 liters of plasticized ethyl cellulose at 3% in acetone. This product was approved by the Quality Control to continue the process of obtainment of the programmed dissolution, as is discussed in the following example 4.

4.- Batch: PE 10326 and 10328 – Second phase

Half the parcel obtained in example 3 was placed in a liquefied bed with Wurster and applied the same ethyl cellulose solution at a rate of 1.5 liters/kg of micro granules. This procedure was repeated with the second half. The mixture of both fractions was encapsulated by dosing in capsules No.1 for 75 mg Venlafaxine Base doses, and in capsules No. 0 for 150 mg Venlafaxine Base doses.

There were obtained products with following features:

| 10326 | 10328 |
|---|---|
| Each capsule contains 74,8 mg Venlafaxine Base | Each capsule contains 149, mg Venlafaxine Base |

| Dissolution: | |
|---|---|
| After 1 hour: | 5.4% |
| After 4 hours: | 46.5% |
| After 8 hours: | 74.8% |
| After 24 hours: | 100.0% |

5.- Batch: 10329 and 10330 – First phase.

3.500 kg of Venlafaxine HC1 were kneaded and applied in an adequate size boiler, on 1.750 kg of sugar and starch core. The binding solution was PVP at 5% in isopropyl alcohol, and were used about 7.000 liters. Once the application of the active principle was over, the obtained product was coated with 1.050 kg of talk. The analytical profile of the product was the following:

Weight: 6.300 kg

Value: 510.5 mg/g

Balance of the drug: 3.216 kg (yield: 91.9%)

Dissolution: 105% in 1 hour

6.- Batch 10329 and 10330 – Second phase.

The product obtained in example 5 was coated in the same coating boiler in which it was elaborated. The solution employed for the coating was constituted of ethyl cellulose in acetone and isopropyl alcohol. The solution was applied on the micro

granules until obtaining a satisfactory profile in dissolution. After that the micro granules were encapsulated in capsules No. 1 for the 75 mg doses and in capsules No. 0 for the 150 mg. Doses. It was obtained capsules containing 73,8 mg and 143,8 mg of Venlafaxine Base, respectively and a dissolution as described next:

| Time | Dissolution |
|---|---|
| After 1 hour | 30,5% |
| After 4 hours | 58,8% |
| After 8 hours | 70,2% |
| After 24 hours | 87.1% |

Bioavailability in humans.

It was conducted a study entitled:

"Comparative study of plasmatic concentrations of Venlafaxine after administering a programmed liberation formulation (1x150 mg), one of sustained liberation (1x150 mg) and one immediate liberation reference (2x75 mg) in healthy volunteers."

Such study was presented at INAME and its results, measured according to the pharmacocinetic AUC tot parameter, allows concluding that the absorption of the product in humans, whose formulation is claimed, is similar to that observed with 2 taken from the reference product (2x75 mg), while it is 28% superior, compared to previous prolonged action formulations [2.279 ng.h/ml versus 1.751 ng.h/ml].

It is also proved that the adverse effects of the formulation being claimed, are reduced by 50% compared to those caused by the reference formulation, due to the plasmatic concentration peak being reduced as it is a programmed liberation formulation.

## Claims

1.- "PROCESS FOR THE PREPARATION OF PROGRAMMED LIBERATION COMPOSITIONS WITH VENLAFAXINEE AND THE RESULTING PRODUCT", comprising mainly a formation of prolonged liberation capsules with the active principle Venlafaxine HC1, wherein it presents improvement in the Bioavailability and for comprising the following elaboration process:

- A first phase of elaboration of non active cores, in which the sugar crystals are placed within a coating boiler to be wetted and after that powdered with corn starch; the obtained spherical micro granules dried in stove and depurator, and then classified by their granulometry.
- A second phase, in which to the non active cores of adequate granulometry, prepared in the previous phase, are aggregated, as binder, a povidone alcoholic solution and, next, the active drug, Venlafaxine HC1, as impalpable powder, and the so obtained micro granules being coated with talk, depurated and dried;
- A third phase, in which it is completed the application of the coat over the micro granules containing the active drug, utilizing ethyl cellulose solutions.
- A fourth and last phase, in which it is made the encapsulation of the coated micro granulated.

2.- "PROCESS FOR THE PREPARATION OF PROGRAMMED LIBERATION COMPOSITIONS WITH VENLAFAXINEE AND THE RESULTING PRODUCT, as claimed in 1, wherein the active principle Venlafaxine HC1 may be found in the final product in a rate of between 10% and 80% by weight.

3.- 'PROCESS FOR THE PREPARATION OF PROGRAMMED LIBERATION COMPOSITIONS WITH VENLAFAXINEE AND THE RESULTING PRODUCT", as claimed in 1, wherein the Povidone utilized as binding in the second phase of the process may be found in the final product at the rate between 1% and 40% by weight.

4.- "PROCESS FOR THE PREPARATION OF PROGRAMMED LIBERATION COMPOSITIONS WITH VENLAFAXINEE AND THE RESULTING PRODUCT", as claimed in 1, wherein the coating of the micro granules with the active drug may be made in a coating boiler.

5.- "PROCESS FOR THE PREPARATION OF PROGRAMMED LIBERATION COMPOSITIONS WITH VENLAFAXINEE AND THE RESULTING PRODUCT", as claimed in 1, wherein the coating of the micro granules with the active drug may be made in liquefied bed with Wurster, previous treatment for the improvement of the mechanical properties.

6.- "PROCESS FOR THE PREPARATION OF PROGRAMMED LIBERATION COMPOSITIONS WITH VENLAFAXINEE AND THE RESULTING PRODUCT", as claimed in 1, wherein for the coating of the granules containing the active drug, acetone solutions, acetone-alcoholic or further alcoholic of ethyl cellulose solutions may be used in a rate between 0.1% and 50% by weight.

7.- "PROCESS FOR THE PREPARATION OF PROGRAMMED LIBERATION COMPOSITIONS WITH VENLAFAXINEE AND THE RESULTING PRODUCT", as claimed in 1, wherein the ethyl cellulose utilized for the coating of the granules may be total or partially substituted by Shellac, Eudragit, Ethers or Cellulose Esters .

8.- "PROCESS FOR THE PREPARATION OF PROGRAMMED LIBERATION COMPOSITIONS WITH VENLAFAXINEE AND THE RESULTING PRODUCT", as claimed in 1, wherein to the ethyl cellulose solutions utilized for the coating of the granules, we may aggregate plasticizers at a rate between 0.01% and 5% by weight in the final product, aiming to avoid the formation of breakable membranes.

9.- "PROCESS FOR THE PREPARATION OF PROGRAMMED LIBERATION COMPOSITIONS WITH VENLAFAXINEE AND THE RESULTING PRODUCT", as claimed in 1, wherein the plasticizers that may be aggregated to the

ethyl cellulose solutions at the coating stage are: Mygliol, Castor Oil, Honeybee Waxes, Phthalic Esters.

10.- "PROCESS FOR THE PREPARATION OF PROGRAMMED LIBERATION COMPOSITIONS WITH VENLAFAXINEE AND THE RESULTING PRODUCT", as claimed in 1, wherein the coating of the granules containing active drug is applied in the proportion needed to get the desired programmed dissolution profile.